

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 5090/WO/98	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IL99/00677	International filing date (day/month/year) 13/12/1999	Priority date (day/month/year) 17/12/1998
International Patent Classification (IPC) or national classification and IPC G01N33/84		
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF THE...		



- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 11/06/2000	Date of completion of this report 06.02.2001
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I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

Description, pages:

1-22 as originally filed

Claims, No.:

1-19 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - ☐ the language of publication of the international application (under Rule 48.3(b)).
 - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☐ furnished subsequently to this Authority in computer readable form.
 - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:
- ☐ the description, pages:
 - ☐ the claims, Nos.:

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☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9, 16, 18, 19
	No:	Claims	10-15, 17
Inventive step (IS)	Yes:	Claims	1-9, 18-19
	No:	Claims	10-17
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

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EXAMINATION REPORT - SEPARATE SHEET**

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Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: F SZURDOKI ET AL: 'Development of Rapid Mercury Assays. Synthesis of Sulfur- and Mercury-Containing Conjugates' BIOCONJUGATE CHEMISTRY, 1 March 1995 (1995-03-01)
- D2: US-A-5 516 697 (KRUZEL MARIAN L) 14 May 1996 (1996-05-14)
- D3: VAN STADEN, J. F. ET AL: 'Determination of total iron in ground waters and multivitamin tablets using a solid-phase reactor with tiron immobilised on Amberlite ion exchange resin in a flow-injection system.' FRESENIUS' J. ANAL. CHEM. (1998) 362(3), 319-323 CODEN: FJACES ISSN: 0937-0633,
- D4: RAMADAN, NABIL ET AL: 'alpha-Aminoacyl hydroxamate adsorbents - a new type of immobilized chelator' J. CHROMATOGR. (1985), 321(1), 81-91 ,
- D5: SINGH S; HIDER R C; PORTER J B: 'A DIRECT METHOD FOR QUANTIFICATION OF NON-TRANSFERRIN-BOUND IRON' ANALYTICAL BIOCHEMISTRY, vol. 186, 1990, pages 320-323, cited in the application
- D6: HERSHKO C; GRAHAM G; BATES G W; RACHMILEWITZ E A: 'NONSPECIFIC SERUM IRON IN THALASSEMIA AN ABNORMAL SERUM IRON FRACTION OF POTENTIAL TOXICITY' BRITISH JOURNAL OF HAEMATOLOGY, vol. 40, 1978, pages 255-264, cited in the application
- D7: EP-A-0 499 712 (KERNFORSCHUNGSZ KARLSRUHE) 26 August 1992 (1992-08-26)
- D8: US-A-5 773 227 (KUHN MICHAEL A ET AL) 30 June 1998 (1998-06-30)
- D9: WO 92 07259 A (BIOMED FRONTIERS INC) 30 April 1992 (1992-04-30)

While the applicant's observations have been considered, the previously expressed opinion is nevertheless maintained for the following reasons:

1. Novelty (Article 33(2) PCT)
 - 1.1 Claims 10-15 and 17 do not meet the requirements of Article 33(2) PCT as they are already disclosed in the prior art.

D2 (see Examples 5-7) discloses biosensors for assaying iron in a sample, wherein lactoferrin is covalently immobilised onto the surface of a cellulose acetate membrane or a nylon membrane. This document appears to be novelty destroying for claims 10, 11 and 13.

D3 (see Abstract and page 320, point 2.4) discloses a solid-phase reactor with tiron immobilised on amberlite ion-exchange resin for the determination of iron. This document appears to be novelty destroying for claims 10, 11, 13 and 15.

D4 (see Abstract) discloses the synthesis and coupling of metal chelating ligands to an epoxy-activated Sepharose 6B support. This document appears to be novelty destroying for claims 11 and 13.

D5 (see Abstract) discloses a method for quantification of non-transferrin-bound iron (NTBI) using an automated HPLC procedure where on-column derivatization with a high affinity iron chelator takes place. This document appears to be novelty destroying for claims 10, 11, 13 and 15.

D6 (see Abstract and page 256, Materials and Methods 3rd paragraph) discloses the determination of unbound iron using DEAE-Sephadex-catechol disulphonic acid columns. This document appears to be novelty destroying for claims 10, 11, 13 and 15.

D7 (see Example 1) discloses a calcein-porous glass sensor for the determination of metal ions. This document appears to be novelty destroying for claims 10 and 11.

D8 (see claim 1) discloses a water-soluble polysaccharide covalently attached to at least one chelating moiety selective for a monovalent or divalent metal ion. This document appears to be novelty destroying for claims 10, 11 and 13.

D9 (see claims 1-20) disclose a composition comprising an adduct of a conjugate of deferoxamine moieties covalently bonded to a polymer. This document appears to be novelty destroying for claims 11-15 and 17.

D1 (see Abstract, page 147 figure 5 and 1st paragraph) discloses a mercury assay based on the competition between mercuric ions and an organomercury conjugate in binding to a chelating conjugate. Neither a surface coated with the polymer conjugated form of metal chelator nor a polymer conjugated to a metal chelator are described in this document.

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- 1.2 Claims 1-9, 16, 18 and 19 appear to be novel, because the known prior art does not disclose their subject-matter.
2. Inventive step (Article 33(3) PCT).
 - 2.1 Claims 1-9 are considered to be inventive. The technical problem to be solved by these claims is the provision of an alternative method for determining the concentration of a non-bound metal ion in a sample. The prior art neither discloses nor suggests the method using a surface coated with a polymer-conjugated form of a metal chelator and a marker conjugated with a moiety that can be captured by the metal chelator, calculating the concentration of the metal ion in the sample from the concentration of binding sites available, after the metal ion of the sample has been captured by the metal chelator, for capturing the metal ion bound to the marker.
 - 2.2 Dependent claim 16 does not contain any technical feature, which in combination with the claim to which it refers, meets the requirements of PCT about inventive step.
 - 2.3 Claims 18 and 19 appear to be inventive. The prior art neither discloses nor suggests the kit for determining a non-bound metal ion comprising a surface coated with polymeric arabinogalactan-DFO or with hydroxyethyl starch-DFO conjugate and a marker conjugated with the same metal ion that is determined.

Re Item VII

Certain defects in the international application

The last sentence on page 22 of the description ("... all without exceeding the scope of the invention) renders the scope of the claims unclear when used to interpret them, thereby resulting in lack of clarity of the claims (PCT Article 6 and Guidelines III, 4.3a). This statement should therefore have been deleted.